

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
24 May 2007 (24.05.2007)

PCT

(10) International Publication Number
WO 2007/058335 A1

(51) International Patent Classification:

A61K 31/397 (2006.01) A61P 3/06 (2006.01)
A61K 31/553 (2006.01)

COMPANY LIMITED, 17-85, Jusohonmachi 2-chome,
Yodogawa-ku, Osaka-shi, Osaka, 5328686 (JP).

(21) International Application Number:

PCT/JP2006/323058

(74) Agents: TANAKA, Mitsuo et al.; AOYAMA & PART-
NERS, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Os-
aka-shi, Osaka, 5400001 (JP).

(22) International Filing Date:

14 November 2006 (14.11.2006)

(81) Designated States (*unless otherwise indicated, for every
kind of national protection available*): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS,
LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY,
MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS,
RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/736,319 15 November 2005 (15.11.2005) US

(71) Applicant (*for all designated States except US*): TAKEDA
PHARMACEUTICAL COMPANY LIMITED [JP/JP];
1-1, Doshomachi 4-Chome, Chuo-ku, Osaka-shi, Osaka,
5410045 (JP).

(84) Designated States (*unless otherwise indicated, for every
kind of regional protection available*): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): NISHIMOTO,
Tomoyuki [JP/JP]; c/o TAKEDA PHARMACEUTICAL
COMPANY LIMITED, 17-85, Jusohonmachi 2-chome,
Yodogawa-ku, Osaka-shi, Osaka, 5328686 (JP). IINO,
Hiroko [JP/JP]; c/o TAKEDA PHARMACEUTICAL
COMPANY LIMITED, 17-85, Jusohonmachi 2-chome,
Yodogawa-ku, Osaka-shi, Osaka, 5328686 (JP). WADA,
Takeo [JP/JP]; c/o TAKEDA PHARMACEUTICAL

Published:

— with international search report

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: USE OF TAK-475 TOGETHER WITH EZETIMIBE FOR TREATING HYPERLIPIDEMIA

(57) Abstract: A pharmaceutical composition useful for a prevention and/or treatment of hyperlipidemia, which comprises com-
bining an effective amount of Compound X and ezetimibe is provided.



WO 2007/058335 A1

DESCRIPTION

**USE OF TAK-475 TOGETHER WITH EZETIMIBE FOR TREATING
HYPERLIPIDEMIA**

Technical Field

5 The present invention is based on the findings that N-
[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-
dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-
3-acetyl]piperidine-4-acetic acid (hereinafter, abbreviated
as Compound X) which is a squalene synthase inhibitor (SSI)
10 and useful as a preventive and/or therapeutic agent of
hyperlipidemia, can potentiate the action of ezetimibe
which is a cholesterol absorption inhibitor and widely used
clinically as a preventive and/or therapeutic agent of
hyperlipidemia at present. Thus the present invention
15 relates to a method for treating hyperlipidemia or the like
in animals or humans by use in combination of Compound X
and ezetimibe.

Background Art

20 Hyperlipidemia refers to a state in which the serum
lipid concentration elevates abnormally. The serum lipid
includes cholesterol, phospholipid, triglyceride (neutral
fat) and the like. Specifically, a clinical issue comes
out when cholesterol and triglyceride is elevated. Many
25 epidemiological investigations have clearly shown that

hypercholesterolemia is one of the three risk factors for atherosclerotic diseases such as myocardial infarction, angina pectoris, cerebral infarction and the like accompanied by hypertension and smoking. Accordingly, proper control of cholesterol level in blood is very important in prevention or treatment of atherosclerotic diseases such as ischemic heart diseases. A HMG-CoA reductase inhibitor, what is collectively called statin drug, has been most widely used clinically hitherto as a medication to lower the blood cholesterol level for prevention and/or treatment of hyperlipidemia.

Current treatment guideline regarding the blood lipid control (NCEP-ATP III, USA, The guideline of Japan Atherosclerosis Society, etc.) suggests a therapeutic target level of less than 100 mg/dl for low-density lipoprotein cholesterol (LDL-C) of patients having high risk for ischemic heart disease development. However, from the recent results of the large-scale outcome test concerning the active LDL-C lowering therapy, it has been shown that furthermore lowering of LDL-C level is effective for lowering a risk of ischemic heart disease development even when LDL-C level is less than 100 mg/dl (PROVE-IT test, TNT test, etc.).

On the other hand, the statin has clinical risk of side effects based on the fact that it is a medicine which

inhibits cholesterol synthesis in vivo by inhibiting the activity of HMG-CoA reductase in the cholesterol biosynthetic pathway and lowering its blood concentration. Specifically, when HMG-CoA reductase is inhibited, not only the biosynthesis of cholesterol but also the biosynthesis of some other components such as ubiquinone, dolichol and heme A, which are necessary for the living body, is also inhibited, so that there are concerns of resulting undesirable side effects (for example, rhabdomyolysis, muscle pain, etc.). Further, side effects such as gastrointestinal disturbance and lowered liver function have been also reported. Therefore, the maximum dosage of statin to be administered (for example, atorvastatin and simvastatin: up to 80 mg per day; pravastatin: up to 40 mg per day; pitavastatin: up to 2 mg per day) has been decided based on the dosage for manifesting hepatic toxicity or muscle toxicity and the safety zone in animals and humans. However, since the administration of statin at the maximum dosage, which has been approved for administration in humans, may have high frequency of such toxicity, the treatment by high dose of statin may not be conducted. Accordingly, in case of administering it for treating hyperlipidemia in practical medication, it is usual that a low dosage is administered to a patient in the beginning and then a higher dosage is administered only when

sufficient results are not obtained at the lower dosage. It is general to avoid high dose administration of statin as much as possible.

5 The cholesterol in the human body are mainly provided by exogenous cholesterol derived from a diet and endogenous cholesterol biosynthesized in liver, and the exogenous cholesterol is perceived to account for about two tenth of total cholesterol (Tamio TERAMOTO, Hyperlipidemia Text, published by Mankoudou). Ezetimibe is
10 a drug which lowers plasma cholesterol by inhibiting cholesterol absorption in small intestine, and not only as a single drug, but also as a combination drug with other drugs which differ in mechanism of action, the effect of combined use is clinically observed (Lipka LJ, Cardiovasc
15 Drug Rev. 2003; 21(4): 293-312).

Disclosure of Invention

Summary of the Invention

20 The present inventors have found unexpectedly in the course of investigating various actions of the Compound X that this compound, when combined with ezetimibe, potentiates an action of lowering cholesterol as compared with individual administration, and completed the present invention.

25 That is, the invention relates to:

(1) A method for preventing and/or treating hyperlipidemia, which comprises administering to an animal or human affected with hyperlipidemia a combination of an effective amount of Compound X and ezetimibe;

5 (2) Use of N-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-acetyl]piperidine-4-acetic acid for the manufacture of a pharmaceutical composition for preventing and/or treating hyperlipidemia which comprises combining an
10 effective amount of N-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-acetyl]piperidine-4-acetic acid and ezetimibe;

(3) A pharmaceutical composition for preventing and/or
15 treating hyperlipidemia, which comprises combining N-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-acetyl]piperidine-4-acetic acid and ezetimibe; and

(4) The method according to the above-mentioned (1),
20 wherein the animal or human affected with hyperlipidemia is a patient affected with familial hypercholesterolemia or a patient affected with hyperlipidemia having a high-risk of ischemic heart disease development.

25 Best Mode for Carrying Out the Invention

Compound X is a known compound disclosed, for example, in JP-A No. 9-136880 (Example 36). Compound X is also described as (1-{[(3R,5S)-1-[3-(acetyloxy)-2,2,-dimethylpropyl]-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-
5 1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}piperidine-4-yl)acetic acid and its proposed International Nonproprietary Name (INN) is "lapaquistat". It has been known that this compound has an inhibitory action on squalene synthase in one step of the cholesterol
10 biosynthetic pathway, and lowers the blood cholesterol level by inhibiting cholesterol biosynthesis, and thus is useful for prevention and/or treatment of hyperlipidemia.

JP-A No. 9-136880 discloses that the compounds of the application including Compound X may be used in combination
15 with other various lipid-lowering drugs or cholesterol-lowering drugs in prevention and/or treatment of hyperlipidemia. However, no mentions have been made of the active effects such as the potentiation of actions by the combined use of both as compared with the individual
20 administration (pharmacological data are not disclosed, either). Furthermore, the combined use of ezetimibe is not specifically described therein.

In addition, WO 2005-012272 discloses that another squalene synthase inhibitor may be used in combination with
25 other various lipid-lowering drugs or cholesterol-lowering

drugs such as ezetimibe in prevention and/or treatment of hyperlipidemia. However, no mentions have been made of the active effects such as the potentiation of actions by the combined use of both as compared with the individual
5 administration (pharmacological data are not disclosed, either).

As for the effects of combined use of Compound X and ezetimibe, the inventors have found that actions and effects are significantly potentiated in an animal model by
10 the combined use of both as compared with the individual administration as shown in the serial pharmacological test results below. Such effects of the combination use of both are said to be unexpected and not assumable from the conventional recognition.

15 From the findings in the animal model described above, it has become possible to bring more potent improvement of serum total cholesterol and LDL cholesterol by using Compound X and ezetimibe in combination for prevention and/or treatment of hyperlipidemia, which can't be achieved
20 by a single administration of ezetimibe or Compound X, and the inventors have reached an invention which is able to achieve medical effects in a human.

Furthermore, by using in combination, not only serum total cholesterol and LDL cholesterol are lowered, but also
25 by Compound X, lowering action of serum triglyceride level

and inflammatory reaction and elevating action of high-density lipoprotein cholesterol which is an antiatherosclerotic factor are potentiated, and also a lowering activity of lipoprotein (a) (Lp(a)) which is a prothrombotic factor can be expected.

It has not been reported so far that a combined use of a squalene synthase inhibitor with ezetimibe can achieve the above-mentioned merits in a human or an animal test. Therefore, the present invention provides a novel use of a squalene synthase inhibitor.

In addition, as a compound having squalene synthase inhibitory action to be used in combination with ezetimibe, preferable examples other than Compound X include 5-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic acid, 5-(3-{[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic acid, 5-(3-{[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]methyl}-1,2,4-oxadiazol-5-yl)pentanoic acid, and a salt thereof.

As for a salt of the above-mentioned compounds, a pharmaceutically acceptable salt or a physiologically

acceptable acid addition salt is preferred. For such salts, for example, inorganic acids (e.g., hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid, etc.) or organic acids (e.g., acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid, etc.) or the like are used. Further, in the case that the compound has an acidic group such as carboxylic acid or the like, the
5 may form salts with, for example, an inorganic base (e.g., an alkali metal or alkaline earth metal such as sodium, potassium, calcium, magnesium, or ammonia, etc.) or an organic base (e.g., tri-C₁₋₃ alkylamine such as triethylamine, etc.).

15

The mode of combined administration of Compound X and ezetimibe to be used in the present invention (administration in combination) is not particularly limited, Compound X and ezetimibe may be combined at the time of
20 administration. Examples of such administration mode include (1) administration of a single preparation obtained by formulating Compound X and ezetimibe simultaneously; (2) simultaneous administration via the same administration route of two kinds of preparations obtained by formulating
25 Compound X and ezetimibe respectively; (3) separate

administration at an interval via the same administration route of two kinds of preparations obtained by formulating Compound X and ezetimibe respectively; (4) simultaneous administration via different route of two kinds of preparations obtained by formulating Compound X and ezetimibe respectively; (5) separate administration at an interval via different administration route of two kinds of preparations obtained by formulating Compound X and ezetimibe respectively (for example, administration of Compound X and ezetimibe in the subsequent order or in the reverse order).

Dosage of ezetimibe can be appropriately selected on the basis of the clinically used dosage. The combination ratio of Compound X and ezetimibe can be appropriately selected depending on a subject to be administered, an administration route, targeted diseases, symptoms, combinations thereof or the like. For example, when the subject to be administered is a human, Compound X may be used with an amount of 0.1 to 200 parts by weight (preferably, 5 to 100 parts by weight) based on 1 part by weight of ezetimibe.

When carrying out the above-mentioned invention, a pharmaceutical composition can be administered in a form of preparation which is prepared by a conventional method using conventional carriers for formulation in suitable

amount, wherein the carriers are suitably selected from, for example, an excipient (e.g., calcium carbonate, kaolin, sodium hydrogen carbonate, lactose, starches, crystalline cellulose, talc, granulated sugar, porous substances, etc.),
5 a binder (e.g., dextrin, gums, alcoholated starch, gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose, Pullulan, etc.), a disintegrating agent (e.g., carboxymethylcellulose calcium, croscarmellose sodium, crospovidone, low-substituted hydroxypropylcellulose,
10 partially pregelatinated starch, etc.), a lubricant (e.g., magnesium stearate, calcium stearate, talc, starch; sodium benzoate, etc.), a colorant (e.g., tar dye, caramel, iron sesquioxide, titanium oxide, riboflavins, etc.), a taste-
masking agent (e.g., sweeteners, flavors, etc.), a stabilizer
15 (e.g., sodium sulphite, etc.), a preservative (e.g., parabens, sorbic acid, etc.) and the like. The
pharmaceutical preparations of the present invention
including the above-mentioned preparations contain Compound
X and/or ezetimibe in an effective amount for treating and
20 preventing diseases. Further, the preparations used in the
present invention may contain other drug ingredients as
active ingredients than Compound X and/or ezetimibe. Such
ingredients are not particularly limited as long as the
object of the present invention is achieved, and can be
25 used in a suitable mixing ratio. Specific examples of the

dosage forms include tablets (including sugar-coated tablets and film-coated tablets), pills, capsules, granules, fine-granules, powders, syrups, emulsions, suspensions, injections, suspended injections, inhalers, ointments, and the like. These preparations are prepared by a conventional method (for example, a method described in Japanese Pharmacopoeia).

Dosage of the preparation of the present invention is varied depending on the administration route, symptoms and age or weight of patients, or the like. In the case of oral administration to an adult patient, it is preferable to administer 10 to 500 mg/day as Compound X or ezetimibe once or in several divided portions. The administration route may be any of oral or parenteral.

Examples

In the following, excellent effects of the combined use of Compound X and ezetimibe will be explained by describing specific pharmacological test results. However, this is one example of the effect of combined use of both, and so the effect of combined use is not limited to the following specific pharmacological effects.

Example: Lowering action of plasma cholesterol by combined use of Compound X and ezetimibe

Test method:

To Hartley guinea pigs (5 weeks-old male, N=6), RC-4 diet containing 0.05% cholesterol and 10% corn oil was loaded for 3 weeks, and was administered orally for 14 days, once a day, a 10-mL/kg dose of the vehicle, Compound X (30 mg/kg) alone, ezetimibe (0.15 mg/kg) alone or combination of ezetimibe (0.15 mg/kg) and Compound X (10 mg, 30 mg/kg). On the morning of the following day after the 14th administration, blood was collected, and the total cholesterol in plasma was measured.

Test result:

Treatment	Total cholesterol level (mg/dL)
Vehicle	58.8 ± 4.4
ezetimibe (0.15 mg/kg)	50.1 ± 2.9
Compound X (10 mg/kg)	53.3 ± 3.5
Compound X (30 mg/kg)	48.0 ± 4.3
Combination of ezetimibe (0.15 mg/kg) + Compound X (10 mg/kg)	38.5 ± 2.5
Combination of ezetimibe (0.15 mg/kg) + Compound X (30 mg/kg)	38.2 ± 1.8

Average ± standard error (N=6)

15 Conclusion:

By the combined use of Compound X and ezetimibe, an additional lowering action of total cholesterol in plasma was observed ($P < 0.01$, two-way ANOVA method).

Industrial Applicability

By the combined use of Compound X and ezetimibe of the present invention, hyperlipidemia of a mammal can be
5 effectively prevented and/or treated.

CLAIMS

1. A method for preventing and/or treating hyperlipidemia, which comprises administering to an animal or human affected with hyperlipidemia a combination of an effective amount of N-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-acetyl]piperidine-4-acetic acid and ezetimibe.
2. Use of N-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-acetyl]piperidine-4-acetic acid for the manufacture of a pharmaceutical composition for preventing and/or treating hyperlipidemia which comprises combining an effective amount of N-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-acetyl]piperidine-4-acetic acid and ezetimibe.
3. A pharmaceutical composition for preventing and/or treating hyperlipidemia, which comprises combining N-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-acetyl]piperidine-4-acetic acid and ezetimibe.
4. The method according to claim 1, wherein the animal or human affected with hyperlipidemia is a patient affected with familial hypercholesterolemia or a patient affected

with hyperlipidemia having a high-risk of ischemic heart disease development.

INTERNATIONAL SEARCH REPORT

International application No

PCT/JP2006/323058

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/397 A61K31/553 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, BIOSIS, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>NISHIMOTO TOMOYUKI ET AL: "Lipid-lowering properties of TAK-475, a squalene synthase inhibitor, in vivo and in vitro"</p> <p>BRITISH JOURNAL OF PHARMACOLOGY, BASINGSTOKE, HANTS, GB, vol. 139, no. 5, July 2003 (2003-07), pages 911-918, XP002403241</p> <p>ISSN: 0007-1188</p> <p>page 917, discussion</p> <p>-----</p> <p>-/--</p>	1-4

☒ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

30 January 2007

Date of mailing of the international search report

08/02/2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Young, Astrid

INTERNATIONAL SEARCH REPORT

International application No

PCT/JP2006/323058

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WIERZBICKI A S: "NEW LIPID-LOWERING AGENTS" EXPERT OPINION ON EMERGING DRUGS, ASHLEY PUBLICATIONS, GB, vol. 8, no. 2, 2003, pages 365-376, XP009036380 ISSN: 1472-8214 page 368, right-hand column - page 369, left-hand column page 370, left-hand column, paragraph 5.2.3	1-4
Y	----- PATEL SHAILENDRA B: "Ezetimibe: a novel cholesterol-lowering agent that highlights novel physiologic pathways." CURRENT CARDIOLOGY REPORTS NOV 2004, vol. 6, no. 6, November 2004 (2004-11), pages 439-442, XP009077425 ISSN: 1523-3782 the whole document -----	1-4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2006/323058

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1 and 4 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.